DETAILED ACTION

1. Formal Matters

A. The Response filed 9/7/07 to the Restriction mailed 8/10/07 has been entered into the record.

B. Claims 1-18, 22 and 23 are pending. Applicants have elected the PPARgamma with a Y473A mutation in the ligand binding domain. Therefore, claims 1-12, 14-18, 22 and 23 are the subject of this Office Action. The Response to Applicants' Traversal appears below.

2. Response to Traversal

A. Applicants argue that the special technical feature of the invention which links all Groups is a mutation in the PPAR ligand binding domain. This argument has been considered, but is not deemed persuasive since the invention is drawn to PPAR alpha, delta as well as gamma domains. Applicants have not identified what common core structures these families have in common with one another. Furthermore, with regard to PPAR gamma, Applicants have not identified which SEQ ID NOs (3, 4, 5, 6) are PPAR gammas, nor, again, what common core structures occur among the elected SEQ ID NO:4. Though Applicants have not specifically recited in their Response that they elect SEQ ID NO:4, **it appears, since Applicants state that claims 4-6 read on the elected invention, that SEQ ID NO:4 was intended to be elected.** Therefore, the Election/Response will not be held non-responsive. Applicants are urged to explain to the Examiner if there is any error in this assumption. **Claim 17 recites "SEQ ID NO:3." However, it appears that the sequence which follows in SEQ ID NO:4**. Again, if this is incorrect, Applicants are urged to inform the Examiner. **If SEQ ID NO:3 was, in fact, intended to be recited in claim 17 and if SEQ ID NO:3 is any sequence other than that comprising SEQ ID NO:4, this claim will be withdrawn as being drawn to non-elected SEQ ID NO:3**.

The Examiner, however, has decided to examine the Tyr473Phe mutation along with the Tyr473Ala mutation. As stands, this Restriction is deemed proper and is, therefore, made FINAL. It is also noted that Applicants have stated the Restriction is an election of species. This is incorrect. The Restriction stated that this was a Restriction and made no mention of a species election.

3. IDS

A. References 8, 9 and 10 on the 1449 filed 9/22/05 have been lined thru since the month and day of the submission have not been cited. Multiple sequences for the same receptor may have been submitted in the cited year. Applicants may submit another IDS with the requested information.

4. Claim Objections

A. Claims 1-12, 14-18 , 22 and 23 are objected to since the term "ligand binding" should be hyphenated.

B. Claims 4-6 and 9-11 are objected to since they recite non-elected amino acid substitutions.

C. Claim 17 is objected to since it recites "SEQ ID NO:3." However, the sequence which follows is not SEQ ID NO:3. It is believed that the claim should recite "SEQ ID NO:4."

DC. Claims 10, 11 and 17 are objected to since they recite both the SEQ ID NO as well as the entire sequence. Amending the claim to recite only the SEQ ID NO is sufficient and preferred.

5. Claim Rejections - 35 USC § 112, first paragraph –enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1, 2, 3, 7, 8, 18 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutated PPAR gamma ligand binding domain polypeptide (and encoding polynucleotides) which can both (1) bind a partial agonist and (2) bind a full agonist to a lesser extent than wild type in which Y473 is substituted with either Ala or Phe (Figures 4 and 5), does not reasonably provide enablement for any other polypeptide meeting the claimed limitations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming all PPAR ligand binding domains which comprise a mutation and which can bind to, and be activated by, a partial agonist and bind a full agonist to a lesser extent than the wild-type receptor. Applicants have only demonstrated that the

PPAR gamma agonist with a mutation at position 473 to convert a tyrosine to either an Ala or Phe is capable of meeting the claimed limitations. Claims such as claim 1 are not limited to the gamma subtype of PPAR receptor, nor are they limited to the Y473 mutation, nor to the Y473 with the specific mutations to Ala or Phe.

The specification only provides guidance and working examples (Figures 4 and 5) of mutations in the PPAR gamma polypeptide. Furthermore, this guidance and working examples only extends to a specific residue, Y473 and to specific mutations of that residue to either Ala or Phe. Given this minimal guidance and working examples, it is not predictable to the artisan as to which other PPAR polypeptides, other than gamma, and to which positions of the gamma polypeptide other than that of Y473 can be altered to meet the claimed limitations. Furthermore, it is not predictable as to which residues other than Ala and Phe residue 473 can be mutated and meet the claimed limitations.

For these reasons, the Examiner concludes that undue experimentation is required to practice the invention as claimed.

B. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 14-16 recite:

> A method of making a mutated PPAR ligand binding domain polypeptide comprising the step of mutating a PPAR ligand binding domain such that an amino acid present in a wild-type PPAR ligand binding domain that makes a direct interaction with a full agonist either makes no interaction, or a substantially different interaction, with said full agonist.

The question that arises is whether the specification has enabled actually visualizing which residue actually comes in contact with ligand, or some other method by which one in the art can verify that the amino acid no longer in contact with a full agonist. The specification provides no guidance of how to determine whether or not an amino acid previously in contact with a full agonist has reduced or absent interaction after a mutation has been made to the PPAR domain. It is possible that the potency or efficacy of a ligand is reduced not by an altered binding to an amino acid in the mutant, but to the interaction with amino acids not previously involved in agonist binding.

Applicants have provided examples demonstrating that the Tyr473Ala or Phe mutation can alter the binding of a full agonist; however, the showing that certain amino acids no longer interact with said agonist has not been demonstrated.

For these reasons, the Examiner concludes that undue experimentation is required to practice the invention as claimed.

6. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 1, 2, 3, 7, 8, 18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. The specification describes mutated PPAR gamma ligand binding domain polypeptide which can both (1) bind a partial agonist and (2) bind a full agonist to a lesser extent than wild type wherein Y473 is substituted with either Ala or Phe (Figures 4 and 5). No other mutation at residue 473, nor any other mutation other than at residue 473 has been show to meet the claimed limitations.

PPAR ligand-binding domains other than Tyr473Ala and Phe would have one or more amino acid substitutions, deletions, insertions and/or additions to the claimed PPAR ligand-binding domain. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the (encoding nucleic acid) or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "PPAR ligand-binding domain" alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

B. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. Claims 14-16 recite:

> A method of making a mutated PPAR ligand binding domain polypeptide comprising the step of mutating a PPAR ligand binding domain such that an amino acid present in a wild-type PPAR ligand binding domain that makes a direct interaction with a full agonist either makes no interaction, or a substantially different interaction, with said full agonist.

The question that arises is whether the specification has provided adequate written description as to which residue actually comes in contact with ligand. The specification provides no description of how to determine whether or not an amino acid previously in contact with a full agonist has reduced or absent interaction after a mutation has been made to the PPAR domain. It is possible that the potency or efficacy of a ligand is reduced not by an altered binding to an amino acid in the mutant, but to the interaction with amino acids not previously involved in agonist binding. The specification only demonstrates that the Tyr473Ala or Phe mutation can alter the binding of a full agonist; however, the showing that certain amino acids no longer interact with said agonist has not been demonstrated.

PPAR ligand-binding domains which meet the claimed limitations, including the Tyr473Ala or Phe mutants, would have one or more amino acid substitutions, deletions, insertions and/or additions to the claimed PPAR ligand-binding domain. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the (encoding nucleic acid) or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "…an amino acid present in a wild-type PPAR ligand binding domain that makes a direct interaction with a full agonist either makes no interaction…" alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

7. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 2, 3 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "selectively binds" or "selectively activates." It is unclear what as to what are the metes and bounds of these terms. No comparison is being made in order to compare the selective binding of the claimed protein to any other protein. Claim 9 is also rejected since it depends from claim 8.

B. Claims 4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how the artisan can determine which residue "corresponds to" tyrosine 473. It would be expected that a protein with at least 473 residues would be a simple matter of identifying the 473'rd residue of that protein. However, if a protein has fewer than 473 residues, it is unclear which residue would "correspond" to 473 of the claimed protein. Furthermore, the Examiner is assuming that "corresponding to" means finding the identical residue (the 473'rd) in another protein. However, in the absence of a definition of "corresponding to" this assumption may be false and this correspondence may be to, for example, a similarity in binding or other activity, not in physical (primary) structure .

C. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "substantially different." The metes and bounds of this term is not known. This is a subjective term and can be interpreted as anywhere from above 0% to 100%. Furthermore, the term can mean that a completely different reaction (e.g. functional activity, downstream effect, second messenger activation, etc) can occur. Therefore, it is not clear as to what is a "substantially different" interaction.

D. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a conclusion step demonstrating how to determine that the test compound is a partial agonist as compared to, for example, a full agonist or antagonist.

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-12, 14-18, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scanlan et al. (US Patent 6,266,622 – reference 1 on the 1449 submitted 9/22/05). The claims recite a mutated PPAR ligand-binding domain wherein the receptor can bind to a partial agonist and also bind a full agonist to a lesser extent than the wild-type receptor. The claims also recite a Tyr473Ala or Phe mutation. The claims also recite transcription factors comprising these domains as well as nucleic acids encoding these domains and factors.

Scanlan teach that nuclear receptors are a superfamily (column 1, lines 27-30) which comprise numerous receptors including PPAR (column 1, lines 38-42). The also teach that the ligand-binding domain (LBD) is important in ligand binding as is choosing a water-inaccessible site (column 2, lines 10-19). Figure 31 of Scanlan shows a single amino acid substitution in an LBD with reduced ligand binding (column 21, lines 31-33). Scanlan also teach that the LBD is the most highly conserved region in the superfamily (column 13, lines 20-29). Finally, Scanlan teach screening methods (column 2, line 63 to column 3, line 42).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to have mutated any amino acid in the LBD, including Y473, of PPAR since Scanlan teach that this region is the most important for ligand binding and that mutation can lead to decreased ligand binding. These are the major limitations of the instant invention. Scanlan also teach polynucleotides encoding these proteins (column 16, lines 5-15)

9. Art of Interest

Though the Examiner cannot make a prima facie case that an organism, such as a mammal, would meet the limitations of claim 1, since the claims do not recite that the PPAR is isolated, the Examiner informs Applicants that the showing of an organism which displays the characteristics recited in claim 1 would likely be prior art.

10. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman, Ph.D. whose telephone number is (571) 272-0888. The examiner can normally be reached on M-Th 10 AM – 7 PM (eastern); alt F 10 AM – 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert Landsman, Ph.D./
Primary Examiner, Art Unit 1647